

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

DIMETHOATE

SB 950 # 039, Tolerance # 204

Chemical Code #: 000216

November 4, 1987

Revised 8/18/89, 11/28/89, 11/05/91, 1/8/96, 6/20/96, 9/17/96, 9/23/98, 1/14/05

I. DATA GAP STATUS

| | |
|------------------------------------|--|
| Combined, rat: | No data gap, no adverse effect |
| Chronic toxicity, dog: | No data gap, no adverse effect |
| Oncogenicity, mouse: | No data gap, no adverse effect |
| Reproduction, rat: | No data gap, possible adverse effect |
| Teratology, rat: | No data gap, no adverse effect |
| Teratology, rabbit: | No data gap, no adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome effects: | No data gap, possible adverse effect indicated |
| DNA damage: | No data gap, possible adverse effect |
| Neurotoxicity, hen: | No data gap, no adverse effect |
| Neurotoxicity, rat | No data gap, no adverse effect |
| Neurotoxicity, developmental, rat: | Possible adverse effect |

Note: Toxicology one-liners are attached.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

NOTE: These pages contain summaries only. Individual worksheets may identify additional effects.

File name: T050114

Revised: H. Green and M. Silva, 8/18/89; Aldous 11/28/89; Kishiyama, Aldous, and Gee, 11/05/91, P. Iyer, 1/8/96, 6/20/96 and 9/17/96, Gee, 9/23/98 and 1/14/05.

Reconciled with DPR records on file as of January 14, 2005. The highest of these record numbers was 215773 (Document 204-154).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 204-055 (parts 1-10), 063 053805, 065991, 065992, "Report on the Study of the Toxicity of Dimethoate in Rats after 24-Month Administration in the Diet." (BASF Dept. of Toxicology, Project No. 70C0326/8241, 10/9/86). Dimethoate, 96.71%, batch 611A, fed in the diet for 24 months with 50/sex/group at 0, 5, 25, and 100 ppm, with an additional 15-20/sex/group for clinicochemical and hematology measurements at 0, 1, 5, 25, and 100 ppm. General Toxicity NOEL = 25 ppm (decreased weight gain, slight anemia). Oncogenicity NOEL > 100 ppm. Plasma ChE NOEL = 25 ppm. Erythrocyte ChE NOEL = 5 ppm. Brain ChE NOEL = 1 ppm in males and 5 ppm in females. Reviewed as unacceptable, upgradeable with possible adverse effect (angiogenic tumors at several sites). (Margolis and Gee, 10/21/87). Re-reviewed with submission of record numbers 065991 (re-evaluation of microscopic slides of spleens and mesenteric lymph nodes from males) and 065992 (discussion and historical control data). Status change to ACCEPTABLE with no adverse effect. (Green & M. Silva 8/15/89). EPA 1-liner: Core Guideline (2/2/89).

CHRONIC TOXICITY, DOG

** 204 - 085 096690 "Dimethoate: 12-Month Dietary Study in Beagle Dogs." (P. Burford, et al., Huntingdon Research Centre Ltd., HRC Report No. DTF 9-G/90835, 3/19/91). Dimethoate Technical, Batch 611A, purity 96.44%, was administered in the diet at concentrations of 0, 5, 20, or 125 ppm to 6 Beagle dogs/sex/group for 52 weeks. There were no mortalities nor clinical signs of toxicity. Ophthalmoscopy was negative, except for lens opacities in one high dose male and in one high dose female, which were possible (equivocal) treatment effects. The most definitive effect was dose-related inhibition of brain cholinesterase (ChE) activity in both sexes at all dose levels. RBC and plasma ChE activities were both statistically significantly reduced at 125 ppm, and RBC ChE activity was often significantly reduced at 20 ppm. In liver, there were increased numbers of sinusoidal cells containing pigment (presumed to be Kupffer cells containing hemosiderin) in both sexes at all dose levels, but without dose-response relationship. There were no strong indications of hemolysis as a major cause of such pigments. The liver pigmentation and brain ChE findings were considered sufficiently noteworthy that CDFA was advised of these findings in advance of completion of the final report (see 078:090993). Neither of these findings warrants flagging this study as a "possible adverse effect", for reasons given in the discussion section of this review. **Acceptable.** (Kishiyama and Aldous, 11/05/91).

204 - 078 090993 Preliminary report of brain ChE effects and liver findings in study 085:096690, above (no separate review).

ONCOGENICITY, RAT

(see combined, record # 053805)

204 - 031 910667 "Bioassay of Dimethoate for Possible Carcinogenicity: Rat." (NCI, report # NCI-CG-TR-4, 1/77), technical grade, no purity stated. Fed at 155 or 310 ppm to 50 males/group and 192 or 384 ppm to 50 females/group for 80 weeks followed by 33 weeks

observation. UNACCEPTABLE (summary only, no data). No adverse effect reported. (Gee 3/11/85)

EPA 1-liner: Oncogenic NOEL > 500 ppm (HDT); Levels tested =250, 500 ppm.

Core Minimum (003640).

ONCOGENICITY, MOUSE

** 204 - 056 (3 parts) 053806 "Report on the Study of the Toxicity of Dimethoate in Mice After 78-Week Administration in the Diet." (BASF Department of Toxicology, project no. 75C0326/8242, 9/24/86) Dimethoate, Test Substance # 82/326, Batch # 611A (supplied by Industria Prodotti Chimici, Italy), $\geq 96.71\%$. Doses of 0, 25, 100, and 200 ppm were administered in non-pelleted feed to 50/sex/group (main study groups) for 78 weeks and to 10/sex/group (interim sacrifice groups) for 52 weeks. Systemic NOEL = 25 ppm (liver changes). ChE NOEL < 25 ppm. Oncogenicity NOEL ≥ 200 ppm. ACCEPTABLE. No adverse effect. (Margolis 9/22/87 and Gee 10/20/87)

204 - 031 038200 (previously 910667), "Bioassay of Dimethoate for Possible Carcinogenicity: Mice." (NCI, report # NCI-CG-TR-4, 1/77), technical grade, no purity stated. Fed at 250 or 500 ppm to 50/sex/group for 94 weeks. UNACCEPTABLE (summary only, no data). No adverse effect reported. (Gee 3/11/85)

REPRODUCTION, RAT

NOTE: A letter from D. Allemang (of the Dimethoate Task Force) to O. Melnicoe (CDFA ---> CDPR) dated Aug. 1, 1990 states that in an ongoing rat reproduction study [147212, 112467], there was an unexpected decrease in the mating performance in all treated F1 groups compared to respective controls. This was the basis for the indication on the first page of this Summary of a "**possible adverse effect**". Aldous, 10/30/91, revised by Gee, 1/13/05.

** **135, 092 147212, 112467** "The Effect of Dimethoate on Reproductive Function of Two Generations in the Rat." (Amanda J. Brooker, et al., Huntingdon Research Centre Ltd., U.K., Report # DTF 11/91154, 10 January 1992) Dimethoate, with a stated purity of 96.44%, was administered in the diet through 2 generations with two litters per generation at nominal concentrations of 0 (Labsure Laboratory Diet No. 2.), 1, 15, and 65ppm with 24 (2nd generation) or 28 (1st generation) Crl:CD⁷(SD) BR VAF/Plus strain rats/sex/group. Cholinesterase (ChE) inhibition (compared with control values) was noted in both sexes for plasma (3% to 14% at 15 ppm and 19% to 41% at 65 ppm), erythrocyte (17% to 48% at 15 ppm and 55% to 70% at 65 ppm), and brain (8% to 32% at 15 ppm and 13% to 71% at 65 ppm). **Possible adverse reproductive effects are indicated:** reduced numbers of pregnant females were noted at 1, 15, and 65 ppm. Reproductive NOAEL = 1 ppm (Reduced number of pregnant females at 1, 15, and 65 ppm in the first mating of the F1 parents). Progeny NOAEL = 15 ppm [Reduced mean pup weights and reduced mean litter sizes (day 1) were reported at 65 ppm]. Parental NOEL = 1 ppm (erythrocyte and brain ChE inhibition in both sexes at 15 and 65 ppm). Previously reviewed as unacceptable, upgradeable upon submission of dose level justification (preliminary study used to set dosing levels), analysis of dosing material and necropsy results for animals that died or were killed prior to scheduled sacrifice (H. Green and P. Iyer, 12/18/95). Data in 135 147212 provided the necessary information and changed the status to acceptable (P. Iyer, 6/20/96).

137 148879 "The Effect of Dimethoate on Reproductive Function of Two Generations in the Rat." (Diane Allemang, of Jellinek, Schwartz and Connolly, Inc., Representative of Cheminova Agro A/S). Copy of the original COA (Certificate of Analysis) for batch #611/A from I.Pi.Ci; copy of test results of reanalysis of the test material at the termination of the study by BASF Aktiengesellschaft, copy of report summary entitled "Identification and determination of Active Ingredient Dimethoate and Impurities in One Batch of technical Dimethoate" and a copy of a report from a re-analysis of batch #611/A conducted under GLP by BASF in 1993 submitted. Supplemental data. No worksheet (P. Iyer, 9/17/96).

204-0154 215773 "Dimethoate: Dietary range finding study in mature male and female rats and their juvenile offspring." (Brooker, A. J. and A. Stubbs, Huntingdon Research Centre Ltd., England, DTF 10/891204, May 2, 1990) In this range-finding study, 10/sex/group were fed diets containing 0, 50, 75 or 100 ppm nominal concentrations of dimethoate (no purity or lot number, no analysis for concentration) for 4 weeks prior to mating. Exposure continued through mating, gestation, and lactation until weaning for F0 animals. At weaning, 2/sex/litter of pups, when possible, were retained (approximately 3 weeks) until week 6 post partum, being fed the same diet concentrations. There were a total of 20 pups/sex/group. Evaluations of F0 animals included food consumption, body weight, clinical signs, limited hematology parameters and plasma, RBC and brain cholinesterase activity. Also, reproductive parameters, including estrus cycling, were evaluated. For retained pups, hematology and cholinesterase activities were evaluated as well as food consumption and body weights. No histology was performed. The results for F0 adults showed no mortality and no total litter loss. There appeared to be a dose-related reduction in implantations and increase in pre-birth loss, resulting in smaller litter size (0: 15.4; 50 ppm, 13.7; 75 ppm, 14.0 and 100 ppm, 13.2). Pup weights were lower than control at weaning at all doses (0, 48.6 g; 50 ppm, 43.7 g; 75 ppm, 40.6 g and 100 ppm, 41.4 g). Signs of reaction to treatment included 3/10 and 6/10 dams at 75 and 100 ppm with intermittent tremors, primarily in the first two weeks post partum. Two of ten females at 100 ppm also showed bulging of the eyes. Cholinesterase activities were affected at all doses in both sexes of adults. RBC and brain activities were more effected than plasma. Statistical analyses were not included. For retained pups, cholinesterase activities were also effected, again with RBC and brain being more effected than plasma. There was no NOEL in either F0 adults or pups for ChE activity. Reproductive NOEL < 50 ppm (pre-birth loss), pup NOEL < 50 ppm (body weight gain, ChE activity), Parental NOEL < 50 ppm (ChE activity). Supplemental study as a range finding study. Although a supplementary study, the pre-birth loss and lower pup gain prior to weaning have been considered possible adverse effects. (Gee, 1/6/05)

** 204 - 0150 215022 " Dimethoate - Two-generation reproduction toxicity study in Wistar rats, administration in the diet." (Mellert, W., J. Hellwig, Chr. Gembardt, K. Deckardt and B. van Ravenzwaay, BASF Aktiengesellschaft, Experimental Toxicology and Ecology, Germany, project 70R0466/99118, August 7, 2003) Twenty-five per sex were fed 0, 0.2, 1.0 or 6.5 mg/kg for approximately 10 weeks before mating. There were two litters per generation with 2 generations. The content of the diet was adjusted weekly based on body weight and food consumption to maintain the target doses/kg. There were no toxicologically significant findings in body weight, food consumption, clinical signs, organ weights, necropsy findings, estrus cycling or sperm measures in adults of either generation. In males at 6.5 mg/kg, there were histological findings in both F0 and F1 generations, consisting of focal vacuolization of the epididymides and, in F1 males, increased severity in cauda epididymides vacuolization, reduced prostate secretion and diffuse epithelial atrophy. There was, however, no effect on reproduction in the rat. Pups from the F1A litters were selected for the F1 parental generation. Maturation measurements of vaginal opening and preputial separation were comparable at the high dose with controls. There were no clinical signs, necropsy findings or other effects at any dose in

pups with the exception of lower mean body weight (and weight gain) in the 6.5 mg/kg pups in the F1B litters only - not repeated in the F2A or F2B litters. There was statistically significant lower activity in both RBC and brain cholinesterase at 6.5 mg/kg and in brain at 1.0 mg/kg, with the effect more pronounced in female adults. Activities of brain cholinesterase in postpartum day 4 F1B and F2B pups were similar at 0 and 6.5 mg/kg except the brain activity in F1B females reached statistical significance (91% of control value). Reproduction NOEL = 6.5 mg/kg (there were no consistent effects on reproduction parameters). Parental NOEL = 0.2 mg/kg/day (lower cholinesterase activity in brain at 1.0 mg/kg, possible treatment-related effects in male reproductive organs at 6.5 mg/kg, both generations). Pup LOEL = 6.5 mg/kg (statistically significant lower brain cholinesterase activity in F1B female pups, day 4 post partum - not in male pups or in F2B day 4 pups). On this basis, a NOEL was not established for pups. There were no other consistent treatment-related findings in pups or F1A pups raised to be parental animals for the F2 litters. ACCEPTABLE. (Gee, 12/2/04)

Note: The two reproduction studies were conducted in different laboratories with different strains of rat, which may, in part, explain differences in results. (Gee, 12/3/04)

REPRODUCTION, MOUSE

204 - 043 037372 "Dimethoate: Successive Generation Studies in Mice." (American Cyanamid Central Medical Department, report # 65-65, 7/20/65) Dimethoate (Cygon), 98.3%, administered in diet at 0, 5, 15, and 50 ppm to 8 males and 16 females/group. NOEL \geq 50 ppm. No toxicity was reported at any dose level. No adverse effect was reported. UNACCEPTABLE, not upgradeable (no analysis of diets, justification for use of mouse vs rat and choice of dose levels not provided, no histopathology data on parents, husbandry problems). (Shimer 12/27/85 and Gee 1/17/86).

EPA 1-liner: no adverse effects on reproduction; no teratogenesis; systemic NOEL > 50 ppm (HDT); Reproduction NOEL > 50 ppm (HDT). Core Minimum (003640).

TERATOLOGY, RAT

** 204 - 038, -044 017133, 037374, "Effect of Dimethoate on Pregnancy of the Rat." (Huntington Research Centre, report # DTF 3/84245, 4/19/84) Dimethoate, 97.3%, administered by gavage in methyl cellulose to 25 female rats/group at 0, 3, 6, and 18 mg/kg/day on days 6 -15 of gestation. All animals were sacrificed on day 20. Maternal NOEL = 6 mg/kg/day (decreased weight gain, clinical observation of tremors, unsteady gait, salivation, hypersensitivity). Developmental NOEL \geq 18 mg/kg/day. ACCEPTABLE. No adverse effect. (Gee 3/11/85).

EPA 1-liner: Teratogenic NOEL > 18 mg/g/day (HDT); Fetotoxic NOEL > 18 mg/kg/day (HDT); Maternal NOEL = 6 mg/g/day; Maternal LEL = 18 mg/kg/day (hypersensitivity, tremors and unsteady gait). Levels tested by gavage in CrL:COBS CD (SD) BR strain - 0, 3, 6 and 18 mg/g/day. Grade: Minimum (003913).

204 - 033 016838 Summary of record # 017133. (Gee 3/11/85)

204 - 037, 044 017132, 037373, "Preliminary Study of the Effect of Dimethoate on Pregnancy of the Rat." (Huntington Research Centre, report # DTF 1/84244, 4/19/84), Dimethoate, 97.3%, tested at 0, 3, 10, and 30 mg/kg/day by gavage in a preliminary study using 6 female Sprague-Dawley rats/group. General toxicity (reduced body weight), and slightly

reduced litter and mean fetal weight at 30 mg/kg/day. No external fetal abnormalities noted. Supplemental to 017133. No adverse effect reported. (Gee 3/11/85)

204 - 033 016839 Summary of record # 017132, 037373.

TERATOLOGY, RABBIT

** 204 - 040, -044 017135, 037376, "Effect of Dimethoate on Pregnancy of the New Zealand White Rabbit (Teratology)." (Huntington Research Centre, report # DTF 4/84247, 4/19/84), Dimethoate, 97.3%, administered to groups of 11-16 female New Zealand White Rabbits at 0, 10, 20, and 40 mg/kg/day on days 7-19 of gestation. Maternal NOEL = 20 mg/kg (reduced weight gain and food consumption); Developmental NOEL = 20 mg/kg (decreased fetal weights noted in high dose group). ACCEPTABLE. No adverse effect. (Oshita and Gee 3/11/85)

204 - 039, -044 017134, 037375, "Preliminary Investigation of Effect of Dimethoate on the New Zealand White Rabbit (Teratology)." (Huntington Research Centre, report # DTF 2/84246, 4/19/84) Dimethoate, 97.3%, tested at 0, 3, 10, and 30 mg/kg/day and at 50 and 75 mg/kg/day in a preliminary study using New Zealand White Rabbits (5-6/group or 2/group for second study). Supplemental to 017135. No adverse effect reported. (Oshita and Gee 3/11/85)

GENE MUTATION

** 204 - 045 037377 "Mutagenicity Testing of Dimethoate (AC 12,880) in the In Vitro CHO/HGPRT Mutation Assay." (American Cyanamid, project # 0423, 1/30/85) Dimethoate (Cygon) 97.3%, lot # 611A, tested at 0, 1000, 1500, 2000, 2700, and 3500 ug/ml \pm rat liver activation for 5 hours; 72-96 and 160-200 hour expression time. No adverse effect on mutation rate reported. ACCEPTABLE. (Shimer and Gee 1/17/86)

204 - 096 117164 "Results of an Ames Test-Mutagenicity Study." The Ames assay was performed using Salmonella strain TA100 with and without S-9 and concentrations of 20, 100, 500, 2500 and 5000 ug/plate. A 2.1 fold increase in revertant colonies was seen at 5000 ug/plate. A confirmatory assay at concentrations of 2000, 4000, 6000 and 8000 ug/plate demonstrated positive responses (2.9 and 2.1 fold increase) both with and without S-9 activation at 8000 ug/plate. For E. coli strain WP2, increases in revertant colonies (2 and 2.6 fold) were seen at 2500 and 5000 ug/plate. In the confirmatory assay, a dose-related positive response was seen at 4000, 6000 and 8000 ug/plate without activation (2.2, 2.4 and 3.8 fold); and a 2.6 fold increase was seen at 8000 ug/plate with activation. All other strains tested negative. Unacceptable (no data) (Iyer, P. 12/4/95).

204- 033, - 045 016837, 038201, 037379 "Mutagenicity Testing of Technical Cygon Systemic Insecticide (Dimethoate) in the Ames Bacterial Test (Salmonella typhimurium and Escherichia coli).". (American Cyanamid Co., Agricultural Research Division, project # 0-796, 11/16/77) Dimethoate technical was tested in S. typhimurium strains TA 1535, 1537, 98, and 100 and in E. coli (WP-2 uvrA) with and without S-9 activation. S. typhimurium tested at 0, 100, 1000, and 10000 ug/plate (disc test also performed); positive controls inadequate to assure assay was working; no adverse effect reported. Positive results were reported in disc assay with E. coli and subsequently quantified in the plate assay at 10, 100, 1000, 5000, and 10000 ug/plate; increased revertants observed at 5000 and 10000 ug/plate. UNACCEPTABLE. Control for +S9 missing, no confirming experiment. Possible adverse effect indicated. (Gee 3/11/85)

EPA 1-liner: No positive mutagenic responses on any plates containing non-toxic doses. Grade: Acceptable (003640).

204 - 045 037380 "Mutagenicity Test Report: Isodimethoate (Ames: S. typhimurium and E. coli) > (American Cyanamid Co., Agricultural Research Division, report # M77-486). Appendix and general protocol for document/record # 033:016837.

Summary: the negative results in the CHO/HGPRT assay and in Salmonella are judged to carry more weight than the positive effect seen with E. coli at very high concentrations. The overall evaluation, therefore, is that the mutagenicity of dimethoate is equivocal and presents no adverse effect for gene mutation. (Gee 10/87). No change in evaluation (Iyer 12/95).

CHROMOSOME EFFECTS

204 - 100 119706 "Sister-chromatid exchanges in human lymphocytes induced by dimethoate, omethoate, deltamethrin, benomyl and their mixture." (P. Dolara et al., Mutation Research, 1992 283: 113-118). Dimethoate and Omethoate induced a dose-related increase in the frequencies of sister-chromatid exchanges (SCEs) in human lymphocytes in vitro (P of regression lines <0.01). The pyrethroid insecticide deltamethrin and the fungicide benomyl, a tubulin venom, induced a modest increase in SCEs (p = 0.053 and p = 0.055 respectively). Mixtures of the four pesticides composed of 43% dimethoate, 43% omethoate, 12% deltamethrin and 1.2% benomyl at concentrations of 41.5 and 83 ug/ml induced dose-dependent increase in SCEs (p<0.01). Small differences between individuals were noted. Low concentrations of these four pesticides that did not increase SCEs when tested alone did result in SCE induction when tested as a mixture. Dimethoate demonstrated a statistically significant increase in SCEs/cell at 80 ug/ml (p<0.01). Supplemental (P. Iyer, 12/7/95).

** 204 - 045 037378 "Micronucleus Test (MNT)." (Pharmakon Research International, Inc., PH 309A-AC-004-84, 3/7/85) Dimethoate CL 12880, 97.3%, lot # 611A, in 0.9% saline administered in a single dose ip to 4 groups (5/sex/group) at 55 mg/kg of body weight. Groups were sacrificed at 6, 30, 48 or 72 hours after dosing. TEM positive control and saline (0.9%) control groups (5/sex/group) sacrificed at 30 hours. No adverse effect (a.i. did not induce formation of micronuclei). ACCEPTABLE. (Shimer and Gee 1/17/86)
EPA 1-liner: the test compound did not induce any significant increase in the number or PCE containing micronuclei from animals treated with single or multiple doses of 55 mg/kg. Grade: Unacceptable (004516).

** 204 - 053 051165 "Dominant Lethal Study with Dimethoate Technical in the Mouse." (Research & Consulting Co., AG, project # 039003, 7/24/85) Dimethoate technical, administered orally, at 0, 5, 10, and 20 mg/kg body weight to 15 male mice/group for consecutive days; each male paired for 1 week with 2 different untreated nulliparous female mice for each of 8 consecutive weeks. Positive controls treated with 80 mg/kg body weight methyl methanesulfonate (MMS). No adverse effect. (Margolis 10/15/87 and Gee 10/19/87)
Note: study was submitted to fulfill the data requirement for DNA/other but does not qualify for that category. (Gee 10/87)

DNA DAMAGE

**** 204 - 080 091318** "Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats In Vitro with Dimethoate Technical." (Rolf Fautz, Cytotest Cell Research GmbH & Co. KG (CCR), Germany, CCR Project 171000, 8/3/90). Dimethoate Technical, purity 96.38%, was assayed in vitro at concentrations of 7.63, 22.90, 76.33, 229.00, and 763.33 ug/ml for its potential to induce DNA damage in primary hepatocytes of male rats. Triplicate cultures were used for scoring for unscheduled DNA synthesis and duplicates for concurrent cytotoxicity. Williams medium E and 2-acetylaminofluorene (positive) served as controls. Autoradiographic technique was used to determine the net number of grains per nucleus after 18 hours of exposure. **Possible adverse effect:** net grains/nucleus increased for the 2 high dose in experiment I and was confirmed by the highest dose in experiment II. ACCEPTABLE. (Kishiyama and Gee, 11/04/91)

204 - 080 091317 "Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats In Vitro with Dimethoate Technical." (Rolf Fautz, Cytotest Cell Research GmbH & Co. KG (CCR), Germany, CCR Project 160007, 7/31/90). Dimethoate Technical, purity 96.38%, was assayed in vitro, at concentrations of 23, 76, 229, 763, or 2290 ug/ml for its potential to induce DNA damage in primary hepatocytes of male rats. L-15 (vehicle) and 2-acetylaminofluorene (positive) served as controls. Hepatocytes were exposed to dimethoate for three hours in the presence of ³H-thymidine in suspension in an orbital water bath. Unscheduled DNA synthesis was determined by isolating the DNA from 6 replicate cultures and counting radioactivity by liquid scintillation counting. **Possible adverse effect:** Dimethoate statistically significantly increased the incorporation of ³H-TdR into hepatocytes in a concentration-related manner. Mean dpm/mg values increased for all treatments in experiment I and were confirmed at the 3 highest concentrations in experiment II. Toxicity to cells was not evident at the highest dose for either experiment, although toxicity was found in the pre-test cytotoxicity test. UNACCEPTABLE AND NOT UPGRADEABLE (method of exposure, length of treatment, method of isolation of nuclei not justified or explained, others in worksheet.) Kishiyama and Gee, 10/31/91.

**** 204 - 089, -093, -139 098517 112898, 112900, 112902, 112903, 163015** "UDS and S-phase response in primary rat hepatocytes after in vivo exposure (in vitro labeling)." (BASF, 8/15/91, author not identified) Dimethoate, batch 611A, 96.41%, was given by oral gavage to Wistar (Chbb = THOM) male rats at 0 (0.5% carboxymethylcellulose or corn oil), 50, 100 or 200 mg/kg body weight in a single dose, 2 - 3 per group. Liver perfusion was started at 4 or 12 hours post dosing. Hepatocytes were isolated and put into culture wells with ³H-thymidine for 4 hours. Unscheduled DNA synthesis was determined by autoradiography. Three slides per animal were scored with about 35 cells per slide examined for a total of 100 cells. To calculate the net nuclear grains, the most heavily labeled area of a nuclear-sized area of cytoplasm was subtracted from the nuclear grain count. There was no indication of induction of UDS using this protocol. The positive control, 2-AAF, was marginally positive at 12 hours but was effective in 4 hour perfusion sample. Unacceptable, not upgradeable (method of calculating net nuclear grains). (Gee, 11/1/91). Reevaluated as upgradeable with a recounting of slides (Gee, 12/11/95). Upgraded to ACCEPTABLE status with submission of the re-evaluation of the slides for net nuclear counts in -139, 163015. (Gee, 9/22/98)

204 - 093 112898, 112900, 112902, 112903 are journal articles that discuss protocol for the in vivo rat hepatocyte DNA repair assay.

NEUROTOXICITY, HEN

** 204 - 085 096689 "Dimethoate: Acute delayed neurotoxicity in the domestic hen." (V. A. Redgrave, C. Gopinath, and A. Anderson, Huntingdon Research Centre Ltd., HRC Report No. DTF 15/901429, 3/25/91). Dimethoate, batch 611/A, purity 96.42%, administered by a single oral gavage (in water) or subcutaneous injection at a concentration of 55 mg/kg to hybrid brown laying hens. Numbers of hens allocated for 21-day observations were 8 vehicle controls, 3 TOCP positive controls, 10 dimethoate (subcutaneous treated), and 24 dimethoate (gavage). The LD₅₀ of dimethoate via gavage had been found to be 55 mg/kg/day. The same dose via subcutaneous route was uniformly lethal (death usually on day 1). Atropine (which was not protective at twice the LD₅₀) was not used in the main study, nor were hens exposed to a repeat treatment plus additional observation. TOCP hens developed signs of ataxia after 13 to 21 days, however dimethoate hens and controls did not. The dimethoate hens suffered 50% mortality (usually on day 1 after dosing), also weight losses among survivors during the first week, with an apparent b.w. rebound during subsequent weeks. Generally 3 hens/group were sacrificed at 4 hr and at 48 hr for brain cholinesterase (ChE) and for neuropathy target esterase (NTE) in brain and in spinal cord. Brain ChE was markedly inhibited at both time periods following dimethoate treatment, but only slightly following TOCP administration. On the other hand, brain NTE was markedly inhibited in TOCP hens, but only slightly in dimethoate hens. Spinal cord NTE was also markedly inhibited by TOCP, but not at all by dimethoate. Microscopic sections of cervical and thoracic spinal cord revealed small but consistent increases in axonal degeneration in TOCP hens, but brain and peripheral nerves were not affected. There were no microscopic treatment effects of dimethoate. Study is **acceptable**, with **no adverse effects**. (Kishiyama and Aldous, 11/04/91).

204 - 039 037381 "Dimethoate: Demyelination Studies in White Leghorn Hens." (American Cyanamid, report # 65-56, 6/25/65) Dimethoate, 98.1%, lot # W-40403-1, administered in feed for 4 weeks to 3 or 6 hens/group at 0, 65, 130 or 260 ppm. Later repeated with 6/group at 130 ppm dimethoate and 6/group at 2000 or 4000 ppm TOCP. No adverse effect reported. (no pathology of nerves reported). NOEL = 130 ppm. UNACCEPTABLE, protocol not suitable for either acute or subchronic toxicity, inadequate number of birds, birds too old (1-2+ years). (Shimer and Gee 1/17/86)

EPA 1-liner: oral LD50 for hen was 50 mg/kg. Repeated treatment at ½, 1/8, LD50 and lower for 4 weeks in diet (65, 130 or 260 ppm) showed no adverse nerve effect. One hen at each dose level died. Hens on 260 ppm lost 13% body weight. NOTE: only 6 hens per group. Grade: Minimum (003640).

204 - 065 070907 "The Potential of Dimethoate to Cause Organophosphate Induced Delayed Polyneuropathy (OPIDP)," was written by Marcello Lotti M.D. (Professor of Industrial Toxicology, University of Padua Medical School, Padua, Italy). He concludes there is enough information currently available in the literature, to assess potential neurotoxic effects of dimethoate. Data indicate that dimethoate and its major metabolite, omethoate, have negligible potential to cause Organophosphate Induced Delayed Polyneuropathy (OPIDP) based on studies in hens and poisoning cases in man. Omethoate inhibits acetylcholinesterase (AChE) and other esterases to a far greater degree than dimethoate (inhibits at > 5-10 mM) in in vitro studies. Omethoate has an I50 for AChE at 150 uM but for neurotoxic esterase (NTE), no inhibition was detectable up to 5 mM. The dose of dimethoate needed to induce OPIDP would exceed the lethal one by 30 times. In vivo studies (not guideline), where dimethoate was fed to hens at near lethal (unprotected) doses, showed no signs of OPIDP up to 3 months after treatment. In another study birds were fed omethoate at doses up to 240 ppm for 4 weeks. No cholinergic effects, clinical or histopathological signs of peripheral neuropathy were observed. Other studies using dimethoate or omethoate in hens showed similar results, however, none were performed according to FIFRA guidelines. Results in humans with poisoning by omethoate

gave conflicting results. Although data demonstrate that there is little risk for OPIDP due to dimethoate, CDFA maintains that a guideline test for neurotoxicology should be performed. H. Green & M. Silva, 8/16/89.

204 - 066 071719 This volume contains an exact duplicate of 070907 as well as a letter and other correspondence from Dr. Giorgio Chiesa, describing the intentions of the Dimethoate Task Force. M. Silva, 8/16/89.

NEUROTOXICITY, RAT

** 204-0152 215771 "An acute neurotoxicity study of dimethoate in rats." (Lamb, I. C., WIL Research Laboratories, WIL-206002, July 27, 1993) Groups of 12/sex (15/sex for the high dose) Sprague-Dawley Crl:CD@BR rats were exposed to a single oral gavage dose of Dimethoate (Lot number 20522-00, 99.1% purity) at 0, 2, 20 or 200 mg/kg. FOB (home cage observations, handling, open field, sensory, neuromuscular and physiological observations) were made pretest (day -7), 2 hours after dosing on day 0 (time of peak activity) and on days 7 and 14. Motor activity were evaluated on this same schedule. Brain weights and dimensions were recorded at termination. Tissues of the nervous system (CNS, PNS) were examined in controls and high dose groups following perfusion preservation, 5/sex/group. At the high dose (200 mg/kg), many effects were noted, including clinical signs (gait alterations, tremors, constricted pupils), colored material on many parts of the body, decreased rearing, impaired hindlimb extensor strength, impaired rotarod performance, reduced forelimb grip strength, lower body temperature, reduced motor activity and others. The clinical signs were seen primarily on day 1 and/or 2 following dosing. There was no effect on brain weight or dimensions and no neurohistopathological findings at 200 mg/kg. At 20 mg/kg, the only finding was treatment-related alteration of pupil response ("no pupil response" to a beam of light). There were no findings at 2 mg/kg, either sex. NOEL = 2 mg/kg/day. Cholinesterase activity was not measured. Acceptable. (Gee, 1/7/05)

** 204 - 0153 215772 "A subchronic (13 week) neurotoxicity study of dimethoate in rats." (Lamb, I. C., WIL Research Laboratories, Inc., Ashland, OH, WIL-206003, February 7, 1994) Sprague-Dawley Crl:CD@BR rats were fed Dimethoate (99.1%) in the diet for approximately 13 weeks at concentrations of 0, 1, 50 or 125 ppm (average intake of 0.06, 3.22 and 8.13 mg/kg/day for males and 0.08, 3.78 and 9.88 mg/kg/day for females). There were 10/sex in the controls, 1 and 50 ppm groups with 12 males and 10 females at 125 ppm. Parameters recorded included clinical signs, body weight, food consumption, and Functional Observational Battery and Motor activity. In addition, plasma and RBC cholinesterase activities were evaluated pretest, and weeks 3 and 7 and at termination. Brain cholinesterase activities of 6 different sections of the brain, with 5/sex/group except for 7 males at 125 ppm, were evaluated at termination. Brain weight and measurements were recorded. There appeared to be a problem with the week 3 cholinesterase assays so weeks 7 and 13 were performed at another laboratory (Battelle). The only clinical sign related to treatment was a finding of "small feces" at 50 and 125 ppm (control males, 6/3, 50 ppm males, 22/8 and 125 ppm males, 148/12. Control females, 34/7, 50 ppm females, 136/10 and 125 ppm females, 197/10). The cumulative body weight gain of high dose males was slightly reduced, being 249g* compared with 296g in controls. Female body weights were not effected. There were no treatment related effects seen in the FOB or motor activity evaluations, which included home cage, handling, open field, sensorimotor, neuromuscular and physiological observations and total and ambulatory motor activity. Plasma and RBC cholinesterase activities were lower at 50 and 125 ppm and brain activity was lower at 125 ppm in some sections of the brain. There was no effect on brain weight or

dimensions. No neuropathology was seen at microscopic examination. NOEL = 1 ppm (small feces, lower cholinesterase activity in plasma and RBC at 50 and 125 ppm, lower brain activity at 125 ppm). Acceptable. No adverse effect [other than related to cholinesterase activity]. (Gee, 1/11/05)

DEVELOPMENTAL NEUROTOXICITY

204 - 145 213149 “Dimethoate, Developmental Neurotoxicity Study in the CD Rat by Oral Gavage Administration.” (D. P. Meyers, Huntingdon Life Sciences, Ltd., Huntingdon Cambridgeshire, England, Report No. CHV 069/003881, 19 October 2001). 24 mated Crl:CD®BR female rats per group received Dimethoate Technical by oral gavage at 0 (water), 0.1, 0.5, or 3 mg/kg/day from gestation day 6 to lactation day 10. Pups were treated at the same doses on lactations day 11 through 21. Dams showed no treatment-related effects on clinical condition, survival, body weight gain, food consumption, gestation length, necropsy findings, brain weights, implantation rate, or functional observational battery (FOB) performance at any treatment level. Pup weights and litter size were decreased (ns) for post natal days (PNDs) 1 through 4 at 3 mg/kg/day relative to controls. Pup weights and clinical signs were not affected by treatment during PNDs 11-21. At 3 mg/kg/day, reduced activity levels in the standard arena at PNDs 4 and 11, slower righting reflex at PND 11, and decreased rearing scores for females during 1 hour activity testing on PND 17 were recorded. No treatment-related activity/performance effects were noted after weaning. No histopathology, brain weight or brain morphometry changes were noted for offspring in the treated groups. Maternal NOEL = 3 mg/kg/day [cholinesterase was not measured]. Offspring NOEL = 0.1 mg/kg/day (increased pup death (0.5 and 3 mg/kg), lower pup weight and altered motor activity prior to weaning at 3 mg/kg). Possible adverse effect: of increased pup mortality through lactation day 4. Developmental neurotoxicity was not indicated. Unacceptable (pages 461 - 509 are missing and no positive control data were included or cited. Possibly upgradeable. (Green and Gee, 10/4/04).

52966 - 0147 213300 “Dimethoate Cross Fostering Study in CD Rats.” (D. P. Myers, Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England, Report No. CHV 089/033185, 2 March 2004). 100, 25, and 50 mated Crl:CD®BR female rats were dosed with Dimethoate Technical (99.1%) by oral gavage at 0 (water), 3 and 6 mg/kg/day, respectively, from gestation day 6 through lactation day 10. On post-natal day 1 (PND 1) (defined as beginning 6 hours after the completion of parturition), dams and offspring were allocated to treatment groups for cross fostering. In the control group, approximately half of the litters containing 12 or more pups were cross-fostered with dams treated at 3 or 6 mg/kg/day. 3 mg/kg/day litters containing 12 or more pups were cross-fostered with control dams and half of the litters containing 12 or more pups at 6 mg/kg/day were cross-fostered with control dams. At 6 mg/kg/day, one dam died (not treatment related) on gestation day 16. Hair loss on one or both maternal forelimbs was increased (22/49) during lactation compared to controls (16/100) at 6 mg/kg. There were no treatment related maternal clinical signs at 3 mg/kg/day. During the lactation period, an increased incidence of maternal restlessness and scattering of offspring on 2 or more days was noted in litters raised by dimethoate treated dams. Additionally, observations made in the hand revealed fewer treated dams showing some resistance or avoidance on removal from the cage on PNDs 4 and 10 at 3 mg/kg/day (3/23 and 5/23) and 6 mg/kg/day (5/45 and 9/45) vs 20/71 and 23/71 for controls on respective days. Dams in both treated groups had lower body weight gain on lactation days 1-7 compared to controls. Mean pup deaths, days 1 - 11, were 0.2, 0.4, 0.6 (untreated dams), 0.4 (3 mg/kg dams) and 1.2 (untreated in utero) and 1.4 (6 mg/kg dams). At 6 mg/kg/day, treatment-related effects on offspring included an increase in mean mortality, a

decrease in weight gain, an increase in the number of pups taking more than 2 seconds for surface righting in the arena (PND 10), increased blood urea levels (also increased at 3 mg/kg/day), and an increase in pups with no milk in the stomach (also at 3 mg/kg/day) in offspring reared by their own mothers or cross-fostered from control mothers during PNDs 1-11. Supplemental. (Green and Gee, 10/7/04).

204 - 0146 213199 "Dimethoate, Dose Finding Study in CD Rats by Oral Gavage Administration Preliminary to Developmental Neurotoxicity Study." (D.P. Meyers, Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England, Report No. CHV/068/000129, 19 October 2001). Ten of 15 mated CrI:CD[®] BR female rats per group received dimethoate technical (99.1%) by oral gavage at 0 (water), 0.2, 3, or 6 mg/kg/day from gestation day 6 through lactation day 10. Subsequently, 2 pups per sex per litter per group were treated from lactation day 11 to 21. The remaining 5 females per group were treated from gestation day 6 through 20, then necropsied. There were no treatment related maternal clinical signs and no deaths. Significant reductions in maternal body weight were noted at 6 mg/kg/day and in body weight gain at 3 and 6 mg/kg/day, through gestation 20. Mean live litter size was reduced at 6 mg/kg/day and mean pup weight for both dosed and undosed pups was reduced from birth through lactation day 21. Pup mortality was also slightly increased to lactation day 4 at 6 mg/kg/day. At the gestation day 20 necropsy, reductions in maternal and fetal plasma cholinesterase (25% maternal, 66% (f) to 75% (m) fetal at 3 mg/kg/day and 57% (maternal), 73% (f) to 79% (m) at 6 mg/kg/day), erythrocyte cholinesterase (78% maternal, 70% (m) to 82% (f) fetal at 3 mg/kg/day and 85% maternal, 87% (f) to 96% (m) at 6 mg/kg/day), and brain cholinesterase activity levels (75% maternal, 22% (m) to 24% (f) fetal at 3 mg/kg/day and 88% maternal, 35% (m) to 42% (f) fetal at 6 mg/kg/day) were noted relative to controls. Dosed pups necropsied on lactation day 21 also showed decreased plasma (39% (m) to 40% (f) at 3 mg/kg/day and 60% (m & f) at 6 mg/kg/day), erythrocyte (60% (m) to 65% (f) at 3 mg/kg/day and 70% (m) to 80% (f) at 6 mg/kg/day), and brain cholinesterase activity levels (42% (f) to 45% (m) at 3 mg/kg/day and 55% (m) to 66% (f) at 6 mg/kg/day). Maternal NOEL = 0.2 mg/kg/day (reduced body weight gain and ChE activity). Pup NOEL = 0.2 mg/kg/day (ChE activity). Supplemental study. (Gee and Green, 11/29/04)

204 - 0144 213148 "Dimethoate, Effects on Cholinesterase in the CD Rat (Adult and Juvenile) by Oral Gavage Administration." (D. P. Meyers, Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England, Report No. CHV/070/012226, 27 September 2001). Nine of 19 mated females per group (groups 1- 4) received Dimethoate Technical (99.1%) by oral gavage at 0 (water), 0.1, 0.5, or 3 mg/kg/day on gestation days 6 through 20. The remaining 10 dams per group were dosed at the same levels on gestation day 6 through lactation day 10. Subsequently, pups from 8 litters per group were dosed from lactation days 11 to 21 inclusive. Another group of 8 mated females (group 5) was maintained untreated throughout the study. One pup per sex per litter from these dams were treated once at each dose level on lactation day 11. Additionally, 8 of 16 unmated (naïve) rats per sex per group (groups 6-9) were treated once at 0, 0.1, 0.5, or 3 mg/kg/day, with remaining animals were treated for 11 consecutive days. Plasma, erythrocyte, and brain cholinesterase activities were evaluated for selected adults, fetuses, and pups. Sampling for groups 1-4 was as follows: at the gestation day 20 necropsy, 8 dams per group and fetuses (blood samples were pooled for all fetuses within each litter, providing one sample per litter); on lactation day 4, two pups per sex per litter; on lactation day 21, one pup per sex per litter; and on post natal day 60, eight pups per sex per group were sampled. All group 5 pups were sampled on lactation day 11. In groups 6-9, 8 rats per sex per group were sampled on day 1 and on day 11 of treatment respectively. There were no treatment related effects on maternal clinical signs, mortality, body weight, body weight change during gestation, and necropsy findings through gestation day 20 for groups 1

through 4. The number of implantations, resorptions, live young, and fetal weights were not affected. Plasma, erythrocyte, and brain cholinesterase activity were decreased ($p < 0.01$) for dams (44%, 58%, and 60% respectively) and for fetuses (43%, 31%, and 33% respectively) at 3 mg/kg/day on gestation day 20. Brain ChE activity was also reduced 10% ($p < 0.05$) at 0.5 mg/kg/day for dams and fetuses and 12% ($p < 0.05$) for fetuses at 0.1 mg/kg/day.

Maternal parameters of groups 1-4 dams allowed to litter were also not affected by treatment.

Pup viability, pup weight gain, and litter size were comparable to controls. Pup plasma, erythrocyte, and brain ChE activity were slightly reduced (7% to 17%) ($p < 0.01$) on lactation day 4 at 3 mg/kg/day. Significant ChE activity reductions ($p < 0.01$) were noted on day 21 (39% (m) and 38% (f) for plasma; 59% (m) and 65% (f) for erythrocyte; and 45% (m) and 42% (f) for brain). At 0.5 mg/kg/day and lower, ChE reductions were less than 14% for brain, 24% for erythrocyte, and 7% for plasma. On post natal day 60, ChE activity levels had recovered and were generally in line with control values.

ChE activity values for group 5 pups treated once on lactation day 11 and sampled the same day were reduced as follows: plasma 19% ($p < 0.01$) (m) and 18% (f); erythrocyte 7% (m) and 26% (f); and brain 17% ($p < 0.01$) (m) and 18% ($p < 0.01$) (f) at 3 mg/kg/day with very slight reductions below that level.

Group 6-9 animals dosed one time had ChE activity reductions of 19% (m) and 12% (f) for plasma, 17% ($p < 0.05$) (m) and 27% ($p < 0.01$) (f) for erythrocyte, and 12% ($p < 0.01$) (m) and 14% ($p < 0.01$) (f) for brain at 3 mg/kg/day and slight to no reduction at the lower doses. After 11 consecutive doses, ChE activity values were reduced ($p < 0.01$) 37% (m) and 21% (ns) (f) for plasma; 58% (m) and 63% (f) for erythrocyte; and 47% (m) and 58% (f) for brain at 3 mg/kg/day with little or no difference from controls at the lower doses.

Maternal and fetal ChE NOAEL = 0.5 mg/kg/day. Pup ChE NOAEL = 0.1 mg/kg/day.

Supplemental. (Green and Gee, 10/4/04).

204 - 0148 213201 "Cheminova's position concerning the appropriate toxicological endpoints for the regulation of dimethoate." (Cheminova, April 8, 2004) This document discusses Cheminova's interpretation of the developmental neurotoxicity study (record 213149), the two-generation reproduction studies (records 215022 and 147212 + 112467), the range-finding study for the developmental neurotoxicity study (record 213199), the comparative cholinesterase study (record 213148) and the cross-fostering study (record 213300). The document presents several points. The first concerns the death of pups in the main developmental neurotoxicity study as: 1) the number of total litter loss at 0.5 mg/kg are "within the expected range based on the new historical control data..." [see tables 2 and 3]; 2) the pup deaths are not related to exposure *in utero* or in the milk but "strongly associated with a failure of the dam to properly nurture her pups...." This latter point is based on the data from the cross-fostering study. A second point involves the use of a benchmark dose (BMD) approach for brain cholinesterase inhibition using data from a number of related studies and comparing populations of rats (adults, pups, etc.). Regarding the motor activity results, Cheminova presents an evaluation of Dr. V. Moser in Table 8 in terms of "no change" (not significant) or an arrow indicating a significant change (lower than control values). In no instance was there a significant increase in motor activity with increasing dose. The conclusion of Cheminova regarding the appropriate endpoint for regulatory purposes is BMD₁₀ for brain cholinesterase, using non-pregnant adult females, which is claimed as protective of other subpopulations including pups (brain ChE and mortality), fetuses, and pregnant dams (page 63). They state that the appropriate length of dosing should be used for acute and for chronic risk assessments. No worksheet. (Gee, 12/3/04)

204 - 0151 215023 "A meta-analysis of pup mortality and cholinesterase inhibition data for dimethoate." (Reiss, R. and D. Gaylor, Sciences International, Inc., September 7, 2004) The document discusses the rationale for using benchmark dose analysis for pup mortality and for

cholinesterase inhibition, using all available data. BMD₅, BMDL₅, BMD₁₀ and BMDL₁₀ were presented. The authors concluded that the BMDL₅ for pup mortality is 0.64 mg/kg by gavage using combined data from 4 studies. By diet, pups were "at least" 6-fold less sensitive. For brain cholinesterase activity, they concluded that the most sensitive population was dams for gavage exposure with a BMDL₁₀ of 0.19 mg/kg, or three-fold lower than for pup mortality. Adult females and pregnant dams showed about the same sensitivity for ChE. In addition, cholinesterase activity was about 2-fold more sensitive by gavage than diet. No worksheet. Supplemental report. (Gee, 12/3/04)

SUPPLEMENTAL

204 -100 119705 "Erythema-multiforme-like contact dermatitis from dimethoate." (D. Schena and A. Barba, Contact Dermatitis 1992: 27, 116-117). A case-report of erythematous dermatitis in a worker accidentally exposed to dimethoate due to breakage of container. (P. Iyer, 12/18/95).